BRIEF DESCRIPTION OF THE FIGURES

[0019] FIG. **1** is drug manufacturing flow diagram;

[0020] FIG. **2** is the chemical structure of α-Artesunic Acid.

DETAILED DESCRIPTION

[0021] The AS parenteral dosage form must be sterile and not produce CO_2 when the AS dissolves. To avoid CO_2 evolution, we used a non-carbonate-containing, physiologically compatible basic medium. We also manufactured our drug product under cGMP.

Dissolution Medium

[0022] The dissolution medium is sodium phosphate buffered solution.

[0023] In addition to avoiding the production of gas, the dissolution medium must rapidly dissolve the AS, produce a solution in which the dissolved AS is sufficiently stable, and yields a solution of physiologically acceptable pH and osmolality. After many trials and errors, we found that a 0.30±0.05 M, pH 8.0±0.3 sodium phosphate solution meets all of the above requirements and is preferred. Slight variations from these values are acceptable.

[0024] The solute in the dissolution medium has been identified as sodium phosphate by spectral and chromatographic evidence. The average phosphate concentration is 0.30 plus or minus 0.05 M. The average solution volume is 11.0 plus or minus 0.5 mL. The average solution pH is 8.0 plus or minus 0.3.

[0025] Preparation of the 0.30M, pH 8.0 sodium phosphate solution, following a USP procedure, was straightforward and under cGMP. Sterile phosphate solution, 0.30 M, pH 8.0, is manufactured by mixing appropriate weights of monobasic and dibasic sodium phosphate in distilled water to a molarity of 0.30 M and pH of 8.0. The phosphate solution is then sterilized by filtration through a 0.22μ filter into 20 mL vials (12.2 mL/vial). The vials are sealed and then stored at room temperature.

[0026] Sterility of the product, achieved through sterile filtration of the phosphate solution and autoclave of the filled, sealed vials, was accomplished smoothly by Afton Scientific Corporation, Charlottesville, Va. 22902. After having met USP requirements for identity of the product, product sterility, endotoxin, solution concentration, volume, pH, osmolality, and particulates, 10,900 vials of this medium were labeled Afton Batch 57804, assigned WR135946; BR18064, and designated as Component Two of our AS dosage form. The USP procedure is found in 2005 USP 28/NF 23, p 2855; Composition of Standard Buffer Solutions, incorporated herein by reference.

Active Component

[0027] The active component is Artesunic Acid (AS), 110 mg/vial, SRI Batch No. 14462-16, from SRI International, Menlo Park, Calif.

[0028] The Chemical Abstracts (CA) Index name for artesunic acid is: butanedioic Acid, [3R-(3α,5a,6,8a,9α,10α,12,12a R*)]-mono(decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl)ester. The CA Registry Number is 88495-63-0, and the molecular formula is $C_{19}H_{28}O_8$. The formula weight of α-artesunic acid is 384.43 g/mol. This name also defines the stereochemistry at C-10 which, according to the CIP convention, is based on the priority of groups attached to C-10. The 10α-designation refers to the O-succinal group oriented back or toward the peroxide bridge. The 10-designation refers to the O-succinal group oriented away from the peroxide bridge. The molecular formula, $C_{19}H_{28}O_8$, corresponds to a molecular composition of C, 59.36%; H, 7.34%; and 0, 33.29%; and a molecular weight of 384.43. α-Artesunic Acid is shown in FIG. **2**.

[0029] The formulation development of the active component AS requires sterilization of the bulk drug. For a sterilization process to be acceptable, not only sterility of the bulk chemical must be shown, but the process must not alter the physical or chemical nature or the stability of the material. The high purity AS bulk drug, a finely milled, white crystalline powder manufactured by Knoll AG, Listal, Switzerland was used.

[0030] An acceptable EtO treatment cycle was developed and employed as follows:

Sterilization of Bulk Artesunic Acid

[0031] The bulk AS was sterilized before dry fill. Gas sterilization was used. Below are the salient points of the method and the determinations for sterility and pyrogenicity.

[0032] Artesunic Acid is treated for one hour at 102 degrees Fahrenheit and 100% humidity. The chamber is evacuated and ethylene oxide is introduced and maintained at constant pressure and 102 degrees Fahrenheit for four hours. The sterilant cycle is stopped; the chamber is evacuated and washed twice with nitrogen and once with air, all at 102 degrees Fahrenheit. Slight variations of this sterilization method are possible.

[0033] A sample of treated AS is chromatographed. Chromatograms for both treated and untreated AS are identical. AS is stable under the conditions of treatment.

[0034] Samples are tested for residual ethylene oxide, ethylene chlorohydrin and ethylene glycol. Neither ethylene chlorohydrin nor ethylene glycol was detected. Ethylene oxide was detected but at levels well below the FDA proposed limit.

[0035] A microbial limits test was performed and validated to determine the inhibitory properties of AS. The test was negative. AS has no inhibitory properties in this test. (USP 27 <61> & <71>).

[0036] Sterility tests were performed to discover the possible presence of bacteria, fungi, and spores. Samples were doped before treatment with a spore strip, bacteria, and fungi. No colony forming units were found in any test. The treated material is sterile. (USP 27 <71>).

[0037] The Limulus Amebocyte Lysate test was performed to determine the endotoxin levels in the treated AS. Endotoxin levels were below the detectable level in the to treated AS. (USP 27 <85>)

[0038] Ethylene oxide is an effective sterilant for bulk artesunic acid. Results from validated sterility tests on sterilized artesunic acid meet USP requirements for sterility testing. Sterilized artesunic acid also meets USP requirements for endotoxins.

[0039] The EtO-treated AS was dry filled into sterile vials. The best mode for this purpose was to use a portable, manually operated powder dispensing machine was purchased from M&O Perry Industries, Corona, Calif. 92880. Owing to the propensity of the AS bulk drug to clump and cling to the metal surface of the machine, characteristics that prevent both complete filling and complete discharge of the machine loads,